REMARKS

Claims 18, 21, 24, 27, 33 and 36-38 are all the claims pending in the application.

Claims 18-20 have been amended to replace the phrase "lipids" with the phrase "phospholipids having C_{14} to C_{22} fatty acid side chains, which fatty acids are >80% wt saturated or monounsaturated." Support for this amendment can be found, for example, in the specification at page 5, lines 17-37.

Thus, no new matter has been added. Entry of the Amendment is respectfully requested.

Information Disclosure Statement

Applicants respectfully request that the Examiner acknowledges PTO Forms SB/08 submitted with the Information Disclosure Statements of September 4, 2008 and April 3, 2009.

Response to Rejections Under 35 U.S.C. § 103(a)

Claims 18, 21, 24, 27, 33, and 36-38 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lang et al. (Biomineralization of Magnetosomes in Bacteria: Nanoparticles with Potential Applications, Microbial Bionanotechnology: biological self-assembly systems and biopolymer-based nanostructures (2006), pages 107-121, hereinafter Lang) and Sanigorski et al. (Platelet and aorta arachidonic and eicosapentaenoic acid levels and *in vitro* eicosanoid production in rats fed high fat diets, Lipids (1996): 31(7), pages 729-35, hereinafter Sanigorski), and Yazawa et al. (Eicosapentaenoic acid-containing phospholipids for Feeds, Jpn. Kokai Tokyo Koho, 5 pp. (1992), hereinafter Yazawa), in view of Makula et al. (as already made of record, Phospholipid Compostion of methane-utilizing bacteria, J Bacteriol. (1978) June 134(3): 771-777, hereinafter Makula), and Koffas et al. (as already made of record, 2002/0137190 Al, hereinafter Koffas).

The Examiner relies on Lang as teaching a microbial biomass, and also asserts that Lang teaches that there is an abundance of phosphatidylethanolamine (PE) in the magnetosome membrane (MM) of the microbe, such as *M. gryphiswaldense.* However, the Examiner admits that Lang does not teach a method by which plasma cholesterol levels are reduced.

In an attempt to rectify this deficiency in Lang, the Examiner cites Yazawa as indirectly establishing the connection between microbial phospholipid, such as PE and the art known anti-cholesterolemic component, eicosapentaenoate (EPA). However, the Examiner admits that Yazawa does not directly teach the correlation of PE and EPA in reducing cholesterol.

The Examiner further recognizes that Lang does not directly teach EPA-containing PE. However, the Examiner asserts that based on the abundance of nutrients that can be extracted from the microbial biomass of Lang, EPA could be reasonably interpreted as an element that may be aggregated with PE.

To further support the rejection, the Examiner also cites Sanigorski. The Examiner alleges that Sanigorski establishes the nexus between the teachings of Lang and Yazawa. In particular, the Examiner alleges that since Sanigorski teaches the beneficial effects of the administration of EPA in animals, it would be obvious to one of ordinary skill in the art to extract PE of Lang, which is further defined by Yazawa as an EPA-containing phospholipid, to achieve beneficial effects in animals (i.e., reducing of cholesterol levels).

The Examiner concludes from the review of these references, that one of ordinary skill in the art would have recognized that the procedure of extracting the microbial lipids from the microbial biomass of Lang, would reasonably aggregate EPA-containing phospholipids (as taught by Yazawa), which would result in lowering of the cholesterol levels of subjects ingesting the particular component.

Makula and Koffas are cited as teaching the limitations of claims 24, 27 and 36-38. As to claims 36-38, the Examiner cites to Makula as disclosing a composition of phospholipids of *Methylococcus capsulatus*, *Methylosinus trichosporium*, etc. Further, the Examiner asserts that *Methylococcus capsulatus* exhibited a phospholipid composition consisting of phosphatidylethanolamine with $C_{16:0}$ and/or $C_{16:1}$ fatty acid side chains, to name a few. Further, with respect to claims 24 and 27, the Examiner admits that Makula neither teaches a utility for phosphatidylethanolamine, nor administration to fish. In an attempt to rectify the deficiency of Makula, the Examiner cites Koffas as teaching administration of different food and feed formulations to fish.

Applicants respectfully submit that the amendment to present claim 18 overcomes the Examiner's proposed combination of Lang and Yazawa and Sanigorski, in view of Makula, and further in view of Koffas because there is no reason of why one ordinary skill in the art would have combined the prior art references, either individually or in combination, to arrive at the claimed invention.

More specifically, in view of the amendment, the teachings of Makula, Koffas and Lang are rendered irrelevant, whereas Yazawa and Sanigorski teach directly away from the present invention.

Makula teaches, as indicated by the Examiner, that certain methanotrophic bacteria contain phospholipids. For example, of the phospholipids found in *M. capsulatus* a majority of the total fatty acid content is $C_{16:0}$ and $C_{16:1}$ fatty acids (around 80%). Further, the bacterial phospholipids comprise varying amounts of phosphatidylethanolamine (PE) and phosphatidylglycerol (PG).

However, Makula does not suggest any medical utility for the bacteria or for any (partially) purified lipid fraction thereof. Accordingly, the results presented in Makula simply disclose that certain methanotrophic bacteria may contain PE and/or may also contain saturated and monounsaturated fatty acids. Importantly, Makula does not teach or suggest a method by which plasma cholesterol levels are reduced. Further, Makula is silent as to the eicosapentaenoic acid (EPA) or docosapentaenoic acid (DHA) content of methanotrophic bacteria. However, it is clear that the phospholipid component cannot comprise a major portion of EPA or DHA, since the major portion comprises saturated and monounsaturated fatty acids.

Koffas discloses a specific strain of *M. capsulatus* (strain 16a) which may be useful, *inter alia*, for production of food materials and for production of terpenoids, carotenoids and exopolysaccharides (see e.g. paragraphs [0010] and [0075] of Koffas). Koffas is silent as to the content of bacterial phospholipids and does not profile the fatty acids of the organism. Furthermore, no medical uses of phospholipids are mentioned or suggested. For these reasons, Koffas is considered largely irrelevant to the claims as amended.

The authors of Lang review bacterial magnetosomes (intracellular compartments containing magnetic crystals surrounded by a membrane and allowing bacteria to respond to magnetic fields). It is disclosed that the magnetosome membrane (MM) of *M. gryphiswaldense* comprises PE and PG as the most abundant polar lipids. It is to be noted that *M. gryphiswaldense* is not a methanotrophic bacterium and that no indication is given in Lang of the proportions of PE and PG in the MM or of their proportions in the total lipid fraction of the organism, i.e., when the cell membrane is also considered. Furthermore, Lang does not suggest any medical use for the MM of *M. gryphiswaldense*, or for any lipid fraction thereof. Lang is

also silent regarding any potential link between microbial lipids and cholesterol reduction and is therefore also considered irrelevant to the clams as presently amended.

Yazawa (HCAPLUS record) appears to suggest the use of EPA-containing phospholipids such as PE for use as anticholesteremic agents. Yazawa discloses potential feedstuff sources which contain EPA-phospholipids, such as bacterial sources (e.g., *Pseudomonas*) and algal sources (e.g., *Chlorella*). However, Yazawa does not teach or suggest methanotrophic bacteria as sources of EPA-phospholipids and is silent as to any potential medical use of saturated or monounsaturated fatty acid containing compositions.

Sanigorski (Abstract) reports the results of experiments to investigate the effects in rats of arachidonic acid-containing high-fat diets enriched with EPA and DHA. The authors report that enriching the diet with n-3 PUFA (polyunsaturated fatty acid, e.g., EPA and DHA) resulted in significant reductions in tissue levels of arachidonic acid and an increase in the n-3 PUFA, particularly EPA. As noted above in relation to Yazawa, Sanigorski does not suggest methanotrophic bacteria as sources of EPA-phospholipids and is silent as to any potential medical use of saturated or monounsaturated fatty acid-containing compositions.

Conversely, the presently amended claims relate to a method of treatment for reducing cholesterol levels by orally administering a composition comprising methanotrophic bacterial phospholipids, which phospholipids have C_{14} to C_{22} fatty acid side chains which are >80% wt saturated or monounsaturated.

Further, in the present application, Applicants disclose that "[q]uite surprisingly microbial phospholipids used have a marked cholesterol reducing effect despite the fact that the fatty acid side chains are predominately saturated or monosaturated and would be <u>expected to increase plasma cholesterol</u>." [Emphasis added]. See Specification, page 5, lines 17-22. In this

respect, the rejection improperly relies upon motivation provided by Lang to combine Yazawa, Sanigorski, Makula and Koffas. That Applicants have discovered that a microbial phospholipid composition comprising predominantly saturated and monounsaturated fatty acids has marked cholesterol-reducing effects is therefore entirely unexpected and in direct contrast to the teachings at the time the present application was filed. Accordingly, one of ordinary skill in the art at the time the present application was filed, would not have understood that microbial phospholipids exhibit marked cholesterol reducing effects, and thus could not have possessed any motivation to combine the cited references to produce a method of reducing plasma cholesterol as instantly claimed.

In this connection, the Examiner is asked to consider that the phospholipid fatty acids of the prior art associated with anticholesteremic effects (see, e.g., Yazawa) are all polyunsaturated fatty acids. Examples of polyunsaturated fatty acids are:

Arachidonic acid	$C_{20:4}$, n-6
EPA	$C_{20:5}$, n-3
DHA	$C_{22:6}$, n-3

In particular, it can be seen that EPA has 5 double bonds, i.e., it is highly polyunsaturated.

Although the skilled person may have been aware that polyunsaturated fatty acids could be administered as anticholesteremic agents, it is considered surprising and unpredictable that compositions which comprise saturated and monounsaturated fatty acids of microbial phospholipids could similarly be administered for this purpose.

As discussed above, neither Lang nor Yazawa teach the administration of saturated or monounsaturated fatty acids of microbial phospholipids as anticholesteremic agents. Thus, the

combination of Lang and Yazawa fails to render obvious claim 18 as presently amended. Similarly, Sanigorski does not teach the administration of saturated or monounsaturated fatty acids of microbial phospholipids as anticholesteremic agents and cannot therefore rectify the deficiencies of either Lang or Yazawa.

Finally, while Makula discloses a methanotrophic bacterium which comprises PE and saturated and monounsaturated fatty acids from phospholipids, Makula does not suggest any medical utility for said lipids or fatty acid fractions thereof. None of Lang, Yazawa, or Sanigorski can rectify this deficiency and thus the presently claimed subject matter cannot be considered obvious over the teachings of Makula.

In view of the above, the Examiner is requested, respectfully, to withdraw the rejection over Lang and Sanigorski and Yazawa in view of Makula and further in view of Koffas.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The U.S. Patent and Trademark Office is hereby directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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